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Effects of Perioperative Hyperglycemia in Patients With Diabetes Compared to Patients Without Diabetes: A Retrospective Study of Treatment and Outcomes

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Abstract

The main goal of this project was to examine the differences in perioperative hyperglycemia treatment received by patients with a diagnosis of diabetes mellitus (DM) and patients without a diagnosis of diabetes (NDM); and how these treatment differences can affect the length of hospital stay. Studies have revealed that, when comparing DM and NDM patients with the same degree of perioperative hyperglycemia, NDM patients suffer worse outcomes. It has been suggested in previous research that this may be because NDM patients receive treatment that does not measure up to the standard of care treatment that DM patients receive. In this project, we study these standard of care discrepancies between DM and NDM patients, in order to examine the difference in postoperative hospital length of stay (LOS).

We conducted a retrospective cohort study, using a subset of data comprised of inpatients who underwent a broad spectrum of surgery types at Nebraska Medicine over a period of twenty months. All patients in the study experienced perioperative hyperglycemia. Roughly half of them were DM patients and roughly half were NDM patients. We performed bivariate regression analysis on all available covariates in the data set in order to find candidates for final linear and logistic regression models. We also performed a time-to-event survival analysis to see if different lengths of stay among the two groups of patients were explained by possible differences in time lags between hyperglycemia trigger and insulin administration. We aimed to find whether aspects of glucose control practices were associated with hyperglycemic NDM patients experiencing longer LOS than DM patients. This information may bolster existing study conclusions and better assist us in understanding barriers to glucose control measures in NDM patients.

Introduction

The average American undergoes a total of approximately 9 surgical procedures over the course of an 85-year lifetime (Lee & Gawande, 2008). Of all surgical patients, 30-40 percent will develop hyperglycemia at some point during the perioperative period; and one in four patients with hyperglycemia will suffer an adverse outcome in the perioperative setting (DeFelice & Thompson, 2016). Multiple studies have identified the link between poorly managed hyperglycemia in the perioperative setting and adverse outcomes, including morbidity, post-operative infections, increased length of hospital stay, and mortality (DeFelice & Thompson, 2016, Kwon et al, 2013, Umpierrez et al, 2011).

Furthermore, the association between perioperative hyperglycemia and adverse outcomes is stronger among patients without diabetes (NDM patients) than patients with diabetes (DM patients), even with similar elevations in blood glucose level (Kotagal et al, 2013; Kwon et al, 2013; Frisch et al, 2010). One possible explanation is that NDM patients with perioperative hyperglycemia receive inferior treatment compared to DM patients. The purpose of this study was to examine the differences in perioperative hyperglycemia treatment received by DM patients and NDM patients; and how these differences can affect the length of hospital stay (LOS). Thus, our main research question was posed: what differences in perioperative hyperglycemia treatment, if any, were associated with the phenomenon that NDM patients experience longer lengths of stay than DM patients?

Importance

Over 50 million inpatient surgical procedures were performed in the United States in 2010 and this number continues to increase every year (Johns Hopkins Medicine, n.d.). The rising number of surgeries each year in the U.S. leads to a relatively large number of complications affecting the general health of the public. Even an incremental of reduction in adverse outcomes for those experiencing perioperative hyperglycemia could help reduce overall healthcare costs in the U.S., and lead to a sizeable reduction in complications affecting the portion of the public who undergo surgery each year.

If this study lends credence to the belief that NDM patients receive inferior treatment that leads to worse surgical outcomes, it may inform changes in hospital systems and provider practices with regard to the standard of perioperative hyperglycemia treatment. If this and other research leads to changes in the SOC for NDM patients experiencing perioperative hyperglycemia, then it stands to reason that inpatient surgical outcomes for NDM patients as a whole will improve. Better outcomes, including decreased length of hospital stay (LOS), could be extremely beneficial to public health in general; as a growing number of the public undergo inpatient surgeries in the U.S. each year. Thus, we believe that the importance of this research project from a patient health and public health standpoint is evident.

Objectives

Our main goal was to examine treatment standards for perioperative hyperglycemia in relation to the length of stay for DM and NDM surgical inpatients. To address this goal, we focused on the objectives of applying descriptive and inferential methodologies according to the retrospective cohort study design. To help us achieve the descriptive methodological objective, we conducted data analyses using *t*-test to compare numerical demographic characteristics between diabetes status groups; and Chi-square test for the categorical characteristics. To achieve the inferential methodological objective, we conducted a multivariate linear regression for the duration of hospital stay (LOS), accounting for patient risk, surgical risk, and other variables that were deemed to be significant in the analysis phase of building our predictive model.

We utilized multivariate linear regression to test the hypothesis that, on average, hyperglycemic NDM patients have longer lengths of stay than hyperglycemic DM patients. We also utilized multivariate logistic regression to test the hypothesis that a lower proportion of NDM patients receive the SOC for hyperglycemia compared to DM patients. Finally, we utilized a multivariate Cox regression for the time from initial blood glucose reading > 140 mg/dL[2] (hyperglycemic trigger) until the administration of insulin therapy. This tested the hypothesis that the mean wait time between the hyperglycemic trigger and administration of insulin is longer for NDM patients than it is for DM patients.

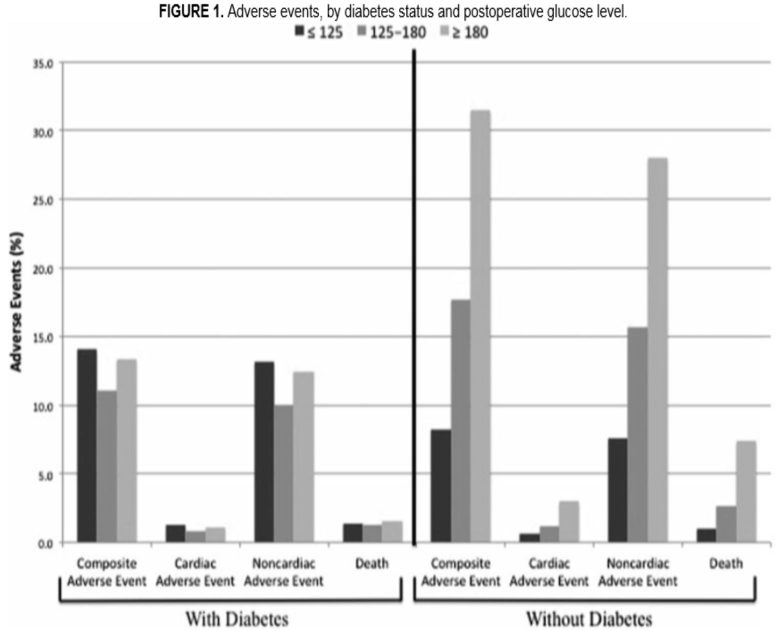
Background

A number of studies show that perioperative hyperglycemia is associated with a host of adverse outcomes (DeFelice & Thompson, 2016, Kwon et al, 2013, Umpierrez et al, 2011). Some studies have focused only on DM patients (Buchleitner et al, 2012; Mcalister et al, 2003; Furnary & Wu, 2004). While others have compared perioperative hyperglycemia in DM and NDM patients (Umpierrez, 2002; Kotagal et al, 2015). Those studies provide evidence that perioperative hyperglycemia has divergent effects on NDM compared to DM patients. This disparity in adverse outcomes has been confirmed for infection, morbidity and mortality. Increased hospital LOS post-surgery has also been found to differ between DM and NDM patients with hyperglycemia (Kotagal et al, 2013). As previously cited from DeFelice and Thompson (2016), 30 to 40% of patients will experience hyperglycemia at some point in the perioperative period. Of those who experience hyperglycemia during the perioperative period, 25% will suffer an adverse outcome. Perioperative hyperglycemia, regardless of diabetes status, has been found to be associated with adverse outcomes in numerous types of surgery, including vascular surgeries, mastectomies and neurosurgeries (Kwon et al, 2013).

A post-operative blood glucose level greater than 140mg/dL[2], representing mild hyperglycemia, is present in as many as 40% of patients undergoing non-cardiac surgery; and 25% of patients with hyperglycemia have a blood glucose level of at least 180 mg/dL[2] (Kwon et al, 2013). Worsening hyperglycemia has been found to be independently predictive of rising mortality (Kwon et al, 2013). Increasing blood glucose levels have been shown to be directly associated with increased hospital costs, wound infections, death and increased lengths of hospital stay (Furnary, Wu & Bookin, 2004). Simha and Shah (2019) found that perioperative hyperglycemia is also associated with pneumonia, sepsis, and cardiovascular events, as well as confirmed its association with increased length of stay and other adverse outcomes.

The phenomenon of NDM patients suffering from higher rates of complications from perioperative hyperglycemia has also been observed repeatedly in the scientific literature. A study by Kotagal et al (2015) found that, although DM patients are at higher risk of adverse outcomes from surgery than NDM patients, NDM patients who develop perioperative hyperglycemia are at even higher risk. Other studies have shown that NDM patients with perioperative hyperglycemia have nearly two times the risk of re-operative interventions, infections, increased length of stay, and in-hospital death than do DM patients (Kwon et al, 2013). The occurrence of death is also shown in a study by Frisch et al. (2010), who noted the increased risk of 30-day mortality following surgery for NDM patients who experienced perioperative hyperglycemia, compared to DM patients who experienced perioperative hyperglycemia. It has been suggested that differences in physiological responses/processes and differences in treatment approach for DM and NDM patients are mechanisms that might help to explain this phenomenon. For example, NDM patients may require a more extreme stress and inflammatory response to result in the same blood glucose elevation than is required for DM patients. Hyperglycemia may also have a more pronounced effect on NDM patients because it is a novel stressor to them. Insulin administration may also be tolerated poorly for a similar reason (Kotagal et al, 2013). Related to this is the fact that insulin therapy might not be used as aggressively, and blood glucose testing might not be used as often on NDM patients. An illustration of the phenomenon of increased adverse outcome rates for perioperative hyperglycemic patients from the study by Kotagal et al (2013) can be seen in Figure 1.

FIGURE 1. Adverse events, by diabetes status and postoperative glucose level.



This same study suggested that the underlying reason for the increased risk of adverse outcomes for NDM patients may be the under-use of insulin for this group. In fact, it is widely noted in the literature that DM patients experiencing perioperative hyperglycemia may receive SOC management more routinely than NDM patients experiencing hyperglycemia. This may be because care providers have a hyperglycemic control regimen planned prior to surgery in patients known to have diabetes. In NDM patients, they likely do not monitor blood glucose as closely and may not focus on hyperglycemia even when it is detected. One study found that glucose measurement only occurred in 59% of hospital patients; with only 54% of those with hyperglycemia receiving insulin therapy at all (Kwon et al, 2013). This seems to lend credence to the belief that NDM patients are simply treated differently than DM patients when it comes to issues related to increasing blood glucose. Confirming this finding, one study found that between the diabetes status groups, NDM patients are simply less likely than DM patients to receive insulin therapy at each increasing blood glucose level (Kotagal et al, 2015). A related issue is the prevalence of undiagnosed diabetes. One phenomenon that has been increasing is that undiagnosed insulin resistance is often not identified until the day of surgery (Kwon et al, 2013). This has been confirmed by other studies that have shown that the diagnosis of diabetes is commonly not revealed until a patient is in the surgical setting. By that time, it may be too late for a medical team to provide hyperglycemia management that is as effective as it is for patients known to have diabetes. Again, in cases of a new diabetes diagnosis, glucose monitoring may not be as timely or as frequent as it is for known DM patients; thus resulting in a higher rate of adverse outcomes (Kotagal et al. 2015).

Appropriate treatment of hyperglycemia appears to reduce the risk of perioperative adverse events. One study concluded that in both diabetes status groups, improvement in the control of blood glucose level has positive effects on mortality and morbidity (Schmeltz et al, 2007). Improved glucose control also reduces the duration of post-operative hospital LOS (Frisch et al, 2010). Other studies suggest that good glucose control is beneficial to reducing post-op mortality and length of stay; and that the SOC to manage perioperative hyperglycemia in DM patients may guide the management of NDM patients (Simha & Shah, 2019). If these problems were noted and tested more often during the pre-operative period, and insulin control was used more often for all patients experiencing perioperative hyperglycemia (regardless of diabetes status), then the rate of adverse outcomes for NDM patients might decrease.

Methods

Among patients in our study cohort, a status of diabetes was defined by a documentation of diabetes mellitus (type 1 or 2) in the medical record at the time of index admission. Length of hospital stay (LOS) was defined as the length of time a patient spent in the hospital from admission time until discharge time, as documented in the medical record. The hyperglycemic trigger was the time at which the patient had an initial blood glucose reading > 140 mg/dL[2]. Insulin administration was defined as the first time basal or short-acting insulin was administered to the patient. In order to study the standard of care for hyperglycemia, we created a dichotomous SOC variable, using the definition of SOC put forth by the American Diabetes Association (ADA, 2016). This states that for the SOC to be delivered in cases of perioperative hyperglycemia, all of the following three criteria must be met: 1) four times daily point of care blood glucose testing ordered within 24 hours of hyperglycemic trigger; 2) basal (long-acting) insulin administered within 24 hours of trigger; 3) short-acting insulin administered within 24 hours of trigger. Finally, patients fell into one of three American Society of Anesthesiologists Physical Status Classifications (ASA Class): mild systemic disease, severe systemic disease, and incapacitating disease.

Increased hospital length of stay (LOS) has been confirmed as an adverse outcome of perioperative hyperglycemia in the scientific literature. Because our final data set had complete and reliable data on this specific adverse outcome, our research focused on LOS. As previously stated, one of our aims was to test the hypothesis that, on average, hyperglycemic NDM patients have longer lengths of hospital stay than hyperglycemic DM patients. Therefore, the statistical inferences we performed focused on LOS as the continuous outcome variable. Another goal was to test the hypothesis that a lower proportion of NDM patients are receiving the SOC for hyperglycemia than are DM patients. Also, whether a possible difference between the two diabetes status groups in the treatment of perioperative hyperglycemia were associated with LOS in our sample of patient records.

For this project, we performed a retrospective cohort study; with data sets provided by the Department of General Internal Medicine (GIM) at the University of Nebraska Medical Center (UNMC) in Omaha, Nebraska. Some of the data sets used were extracted directly from the Electronic Medical Record (EMR); and some were generated through direct chart review completed by a member of the GIM team. This chart review data was collected and managed using REDCap electronic data capture tools hosted at UNMC. REDCap service and support is provided by the Research Information Technology Office (RITO), which is funded by the Vice Chancellor for Research. All data files were exported to Microsoft Excel. We merged all applicable data sets into one final set with one record per Medical Record Number (MRN). The task of importing, cleaning and merging of the separate data files was performed using SAS 9.4 (SAS Institute, Carrey, NC). SAS was also used to perform all of our statistical analyses. For inclusion into our final data set, patients met all of the following criteria: they underwent a surgical procedure at Nebraska Medicine between December 1, 2016 and August 31, 2017; they experienced a perioperative glucose reading of at least 180 mg/dL[2]; they were at least 19 years of age during the perioperative period; and they were admitted to the hospital as a result their surgery and had a length of stay of at least 72 hours.

The study was powered for our main research hypothesis, which was to explore the effect of diabetes status on LOS. For the power and sample size calculations to help us determine a sufficient record count for each diabetes status group, we used the two-sided, un-paired t-test, for power of 80% (0.8) and level of significance, 0.05. Both needed power and group sample sizes were satisfied with our final data set; including 507 total patient records (n_1 = 268 DM patients; n_2 = 239 NDM patients).

Since data extraction was already completed, it was not part of this project. However, the merging of the data and the creation of SOC component and dichotomous variables based on ADA criteria was paramount to the success of the project. Statistical modeling included multivariate linear regression for our continuous response variable (LOS), and multivariate logistic regression for our dichotomous response variable (SOC). The time-to-event (insulin administration) analysis was completed using the Kaplan-Meyer approach and the extended Cox regression model. Where appropriate, transformation of some continuous variables was performed, so as to meet linear regression modeling assumptions. Multivariate linear, logistic and extended Cox regression model results are summarized in subsequent tables and in the forthcoming results section. The level of significance in our final models was capped at alpha = 0.05.

Finally, the linear regression analysis for LOS was consistent with previously published studies. Many studies referenced in the background section performed linear regressions to examine associations between covariates and LOS. We have noted that LOS is highly skewed; and therefore discussed the best way to handle LOS as an outcome. We found one study that, rather than using linear regression on LOS, they used Poisson and negative binomial regression (Carter & Potts, 2014). However, we found that many of the resources we previously cited used linear regression for LOS analysis, as well as additional studies we researched (Taiwo et al, 2016; Szafranski et al, 2014). We also found a specific example of transforming LOS in bivariate and multivariate linear regressions, similar to our approach for this study (Freidl, Benda & Friedrich, 2015). Thus, literature precedence and statistical experience make us confident in how we handled LOS in our analyses.

Statistics

Final models used to address our research hypotheses were derived from multivariate linear regression, multivariate logistic regression, and multivariate extended Cox regression analysis. In order to find covariates to test for inclusion into our linear regression model, we performed bivariate linear regression analysis for each notable continuous variable in our data set independently, with LOS being the outcome variable. We ran single and multifactor Analyses of Variance (ANOVA) to compare all categorical covariates independently with LOS. All variables with a p-value less than or equal to 0.20 were considered viable for testing in our regression models.

To answer our hypothesis regarding whether or not NDM patients have significantly longer lengths of stay than DM patients, we performed a multivariate linear regression. Our initial regression to test this hypothesis started with all of the candidate variables from the bivariate analyses. We then used manual backward selection, which involved removing the covariate with the highest p-value, rerunning the model without said covariate, and repeating this process until the model included only statistically significant variables at the $\alpha = 0.05$ level.

To test our hypothesis regarding whether or not NDM patients received a significantly different standard of care than DM patients, we performed a multivariate logistic regression. This model looked at the dichotomous SOC variable as its outcome. As previously mentioned, all three components of SOC needed to be delivered in order for us to consider that a patient received the SOC for hyperglycemia. If only one or two components of SOC were delivered, we determined that the patient did not receive the SOC for hyperglycemia. We took all of the candidate variables from the bivariate regressions mentioned before and once again used backward selection to obtain our multivariate logistic regression model. We removed all covariates, one by one, until we were left with only the significant covariates (again, based on the $\alpha = 0.05$ significance level). Individual Chi-square and t-tests that showed significant differences between diabetes status groups also provided us with more candidates to examine during our logistic regressions.

We performed an extended Cox regression analysis to help us address our final hypothesis regarding whether or not NDM patients waited significantly longer to receive insulin after hyperglycemic trigger than DM patients. We calculated the number of minutes between the time of hyperglycemic trigger (the point at which the first hyperglycemic blood glucose level was measured in the perioperative period) and the time of first insulin administration. We also calculated the time between the hyperglycemic trigger and hospital discharge. Our time-to-event analysis used this time difference as the outcome variable. For those patients that did not receive insulin (i.e. they did not have an insulin administration time), the time to censoring was the length of time from trigger to hospital discharge. For the predictor variables, we started with some that were deemed to be clinically important, as well as some variables that were deemed significant in the final multivariate linear and logistic regression models. An automatic backward selection for the Cox regression was run until we again were left with only significant factors at the $\alpha = 0.05$ significance level.

For each of the regression model processes, we tested certain clinically indicated one-way interaction terms. Individual statistical tests were examined to interpret the true effects of these interactions (almost all of which were found to be statistically non-significant). It was determined that no interactions warranted inclusion into any of our models. In addition to testing interactions in each of our models, we used other statistical tests, diagnostic tools, AIC values and Adjusted R^2 values to help us find the models that were best-suited to help us address our hypotheses.

Results

Important data set component variables are summarized as means, medians, and standard deviations for continuous covariates; and as counts and percentages for categorical covariates. *P*-values are associated with the differences between the two diabetes status groups. Some factors of interest that we examined, as well as the factors that were significant in each of our models, are shown in Table 1.

Table 1. Characteristics of Important Study Cohort Variables by Diabetes Status

	No Diabetes (N = 239)		Diabetes (N = 268)		
	Mean (SD)	**Median**	**Mean (SD)**	**Median**	**P-value**
Age at Admission	61.55 (15.79)	65.00	62.79 (11.7)	64.00	0.319
Procedure Duration (Hours)	4.86 (2.86)	4.08	3.87 (2.39)	3.11	<.0001
	Count	**%**	**Count**	**%**	**P-value**
Gender - Male	134	56.07	143	53.36	0.541
Race					0.430
White or Caucasian	216	90.38	234	87.31	
Black or African American	8	3.35	19	7.09	
American Indian/Alaska Native	1	0.42	1	0.37	
Asian	2	0.84	1	0.37	
Native Hawaiian\Pacific Islander	1	0.42	1	0.37	
Other	11	4.60	10	3.73	
Unknown	0	0.00	2	0.75	
ASA Class					0.0004
Incapacitating Disease	77	32.22	68	25.37	
Severe Systemic Disease	125	52.30	180	67.16	
Mild Systemic Disease	18	7.53	5	1.87	
Steroids w/i 24 Hours of Surgery (Yes)	147	61.51	143	53.36	0.027

Study results were divided into sections for each of our three hypotheses. Overall, our final data set (n = 507) was evenly divided between DM patients (n = 268) and NDM patients (n = 239). The study cohort contained a slightly larger number of males (n = 277) than females (n = 230); but there was no significant gender differences between the diabetes status groups. The mean age of patients in the cohort was 62 years (SD = 13.8 years); with patients ranging from 19 to 93 years of age. Also, by far the largest race portion of the study cohort (95.46%) was white or Caucasian (n = 450). Interesting to note (and a good indicator as to the even distribution of our study cohort) was that there was no statistically significant difference between DM and NDM patients for age ($p = 0.319$), gender ($p = 0.541$) and race ($p = 0.430$). In our study cohort, 47.14% of all patients (n = 239), regardless of diabetes status, received the SOC for perioperative hyperglycemia; with 48.13% of DM patients (n = 129) and 46.02% of NDM patients (n = 110) receiving the SOC. Some components of the SOC for hyperglycemia variable were significantly different between DM and NDM patients. However, when examining if all three components of SOC were delivered (and thus, whether or not the SOC for hyperglycemia was delivered), there was no statistically significant difference between DM and NDM patients ($p = 0.657$). Other interesting things we noticed will be described in the results for each particular model.

Length of Stay (LOS) Outcome – Multivariate Linear Regression

Our first hypothesis examined if NDM patients had significantly longer average hospital stays than DM patients. Looking at the diabetes status factor in our study cohort data set, we found that the median LOS for DM patients in our sample was 132 hours (SD = 159.93); while the median LOS for NDM patients was 174 hours (SD=242.01). Testing the significance of the difference in the LOS distribution between groups, we considered that LOS was not normally distributed and we ran a nonparametric Mann-Whitney U test. The test results indicated that there indeed was a statistically significant difference between the underlying distributions of LOS for DM and NDM patients ($p < .0001$). See the Appendix for box plots of the Mann-Whitney U test on LOS by diabetes status. Important to note is the presence of outliers in the cohort, as a handful of patients had an LOS of 1,000 hours or longer. We have tried to take this into consideration in our multivariate regression model by accounting for procedure length in hours, which acts as a surrogate for surgery type. Thus we can take into account the lengths of stay for those who had more serious and dangerous procedures. Therefore, we believe our model accounts for these outliers by controlling for the seriousness of the surgical procedure.

There were several factors from bivariate analyses that were statistically significant predictors of LOS; and thus became candidates for our final model. Our subject matter expert determined that many of these variables would likely be highly correlated with our main predictors. For example, there were several different insulin-related variables that were independently significant predictors of LOS, such as those representing the different types of insulin administered. Since insulin-related variables were basically a subset of our dichotomous SOC variable, it was decided to only look at that overall SOC variable, and none of its related components. Similar logic was used to make cases for omitting several other factors that were initially qualified for inclusion in our final regression model. Also of note is that factors such as gender, race, ethnicity, age and smoking status were all non-significant predictors of LOS from our bivariate analyses. Thus none of these factors were included in our final, multivariate regression model. With all that in mind, some important significant predictors of LOS from the bivariate analyses follow. Surgical procedure duration in hours was independently significant ($p < .0001$) in bivariate regression with LOS. In addition, steroid administration during hospital stay ($p = 0.026$), steroid administration on the day of surgery ($p = 0.033$), standard of care delivery ($p = 0.022$), and diabetes status ($p < .0001$) all were significant in bivariate regression with LOS. The final model included the following significant variables that affect LOS: diabetes status ($p < .0001$), standard of care provided ($p = 0.0002$), steroids given on day of surgery ($p = 0.0086$), and procedure duration in hours ($p < .0001$). Model goodness-of-fit plots can be found in the Appendix as well.

These results support our conjecture that NDM patients have significantly longer median LOS than DM patients. In other words, we found that, when controlling for SOC administration, steroid administration on the day of surgery, and length of surgical procedure, DM patients had shorter LOS than NDM patients. The SOC variable was also significant in the model ($p = 0.0002$). This meant that when we controlled for diabetes status, procedure length and steroid administration on the day of surgery, the absence of the delivery of the SOC for perioperative hyperglycemia caused a longer-duration LOS than it would have been had SOC been delivered. Since we hypothesized that both diabetes status and SOC would have an effect on LOS, and both factors were significant predictors of hospital LOS, it appears we have statistical evidence supporting our hypothesis.

Standard of Care (SOC) Outcome – Multivariate Logistic Regression

As previously noted, in order for the SOC to be delivered in cases of perioperative hyperglycemia; (i) four times daily point of care blood glucose testing must have been ordered within 24 hours of hyperglycemic trigger; (ii) basal (long-acting) insulin must have been administered within 24 hours of trigger; and (iii) short-acting insulin must have been administered within 24 hours of trigger. A patient was deemed to have been delivered the SOC for hyperglycemia only if all three of the above events, (i) – (iii), occurred, according to the medical record. If only one or two of these actions were taken, it was determined that the SOC for hyperglycemia was not delivered.

Our second hypothesis aimed to see if there was a difference between DM and NDM patients in how often they received the standard of care for hyperglycemia. Specifically, we wanted to see if NDM patients received the standard of hyperglycemia care less often than DM patients. In our full data set, the total number of patients receiving the standard for perioperative hyperglycemia care was 239 (47.1%); which meant that 268 patients (52.9%) did not receive the SOC. We did find that the SOC was delivered fairly equally among diabetes status groups. A similar number and percentage of DM patients ($n = 129$; 48.1%) and NDM patients ($n = 110$; 46%) received SOC treatment for their hyperglycemia; while a similar number and percentage of DM patients ($n = 139$; 51.9%) and NDM patients ($n = 129$; 54%) did not receive SOC treatment. The estimated odds ratio (OR) of DM patients vs. NDM patients who received the SOC was 0.919 ($p = 0.635$). Thus, surprisingly we found that there was no statistically significant difference regarding the delivery of SOC for perioperative hyperglycemia between the diabetes status groups.

The first component that makes up our SOC variable (whether or not basal insulin was administered to the patient within 24 hours of hyperglycemic trigger) was not a statistically significant predictor, since the OR of DM patients versus NDM patients was 0.854 ($p = 0.377$). In addition, we found that 50.4% of DM patients ($n = 135$) and 46.4% of NDM patients ($n = 111$) received basal insulin within 24 hours of hyperglycemic trigger. Next, we looked at the component of SOC delivery that asked whether or not short-acting insulin was administered to the patient within 24 hours of hyperglycemic trigger. In relation to diabetes status groups, we found that 82.8% of DM patients ($n = 222$) received short-acting insulin within 24 hours of hyperglycemic trigger; whereas only 64.4% of NDM patients ($n = 154$) received this component of SOC. The OR of DM patients vs. NDM patients who received short-acting insulin within 24 hours of trigger was 0.375 ($p < .0001$). In this case, we indeed found a statistically significant difference between DM and NDM patients. The third and final component of SOC delivery was whether or not blood glucose monitoring was ordered for the hyperglycemic patient within 24 hours of trigger. Testing this component, we found similar results to the short-acting insulin component. In relation to diabetes status groups, blood glucose monitoring was ordered for 89.9% of DM patients (n = 241); while only 76.2% of NDM patients (n = 182) received this component of SOC. The OR of DM patients vs. NDM patients who received blood glucose monitoring within 24 hours of trigger was 0.358 ($p < .0001$). Once again, we found an SOC component where there was a statistically significant difference between DM and NDM patients. This means that there were significant differences between diabetes status groups for two of the three components of SOC delivery for hyperglycemia. However, as we have mentioned, all three components must have been delivered to meet the SOC requirement. We somewhat surprisingly found that there just was not a significant difference between diabetes status groups when all three of the SOC components were considered together.

In our final model (with details shown in Table 2), we found that similar variables that were significant in our multivariate linear regression model were also significant in our

Table 2. Summary of Multivariate Logistic Regression Model - SoC Outcome

	Estimate	Standard Error	P-value	OR Point Estimate	95% Wald Confidence Limits	
(Intercept)	-0.8440	0.3395	0.0129			
Diabetes Status (Without Diabetes)	-0.0904	0.1141	0.4280	0.835	0.534	1.305
Procedure Duration (Hours)	0.1086	0.0429	0.0115	1.115	1.025	1.213
Steroids w/i 24 Hours of Surgery (No)	0.4493	0.1118	<.0001	2.456	1.584	3.807
ASA Class[1]						
Incapacitating Disease	1.9116	0.2988	<.0001	40.233	8.403	192.635
Severe Systemic Disease	-0.1285	0.2817	0.6482	5.231	1.134	24.136

OR - Odds Ratio
ASA Class - American Society of Anesthesiologists physical status classification
[1]As compared to the Mild Systemic Disease class

multivariate logistic regression model. Procedure duration in hours (OR = 1.115; CI = 1.025 - 1.213; p = 0.0015) and steroid administration on the day of surgery (OR = 2.456; CI = 1.584 - 3.807; $p < .0001$) were both significant in the final model. An additional factor, the American

Society of Anesthesiologists Physical Status Classification (ASA class), was also significant. ASA class was the only multi-category variable that was significant in any of our final models. The OR for patients in the incapacitating disease class compared to patients in the mild systemic disease class was 40.233 (CI = 8.403 - 192.635; $p < .0001$). The OR for patients in the severe systemic disease class compared to patients in the mild systemic disease class was 5.231 (CI = 1.134 - 24.136; $p = 0.648$). The overall ASA class variable had a p-value $< .0001$; thus indicating that, when controlling for diabetes status, duration of procedure, and steroid administration, ASA class is significantly associated with SOC delivery. Surprisingly, diabetes status was not significantly associated with SOC delivery: the OR was 0.835 (CI = 0.534 - 1.305) and the p-value was 0.428. Again, we found this surprising, given that this hypothesis centered on the belief that DM patients receive a different standard of hyperglycemic care than NDM patients. However, our final model (with forced inclusion of diabetes status) showed us that at least in our cohort, diabetes status was not significantly associated with whether or not a patient received the standard of hyperglycemic care.

Time to Insulin Administration Outcome

Our final hypothesis examined whether or not NDM patients had to wait longer for insulin administration after hyperglycemic trigger than DM patients. For this, we performed a time-to-event analysis. We looked at the difference (in minutes) between the time of hyperglycemic trigger to insulin administration as our time to event. We performed a log-rank test to see if there was a significant difference in the time it took for insulin to be administered to hyperglycemic DM patients and to hyperglycemic NDM patients. We found that the median time from hyperglycemic trigger to insulin administration for DM patients (after censoring those without insulin administration times) was 371 minutes. We also found that the median time from hyperglycemic trigger to insulin administration for NDM patients was 4,122 minutes. This is obviously quite a large difference. The low median for DM patients takes into account the fact that, since these patients had diabetes, oftentimes insulin would be administered before there was even a hyperglycemic trigger. Although many of the DM patients did not receive insulin until after their trigger, many indeed received insulin long before; hence the low time difference median. The high median time from trigger to insulin administration may be due to a couple of outliers in the study cohort who received insulin 15,025 minutes and 25,837 minutes after hyperglycemic trigger. But more important than focusing on the outliers is the fact that the average time from trigger to insulin administration is much longer for NDM patients than it is for DM patients. To check the statistical significance of this difference, we performed a log-rank test. The results showed that the difference between DM and NDM patients in time to insulin administration was indeed statistically significant ($p = 0.0166$). Since the difference was significant and the median time to insulin administration was so much higher for NDM patients, we uncovered some evidence to support the fact that hyperglycemic NDM patients generally wait longer to receive insulin after first measured hyperglycemia than DM patients.

The time-to-event model involved the time from hyperglycemic trigger to first insulin administration, regardless of the type of insulin administered (basal or short-acting). Looking separately at those individual insulin types, we found something similar to what we saw previously. Regarding basal insulin, we found that the median time from trigger to basal insulin administration for DM patients was 1,371 minutes. While the median time from trigger to basal insulin administration for NDM patients was 3,851 minutes. Just as before, there was quite a longer median time that NDM patients waited for basal insulin administration than the time waited for DM patients. This difference between groups was not statistically significant (p =

0.071). Looking at the time difference from hyperglycemic trigger to first short-acting insulin administration, we saw similar results. The median time for DM patients was 401 minutes; while the mean time to short-acting insulin administration for NDM patients was 381 minutes. Once again, the difference between groups was statistically significant ($p = 0.0042$).

Finally, we tested an extended Cox regression model to find variables that may have been associated with an increased time from hyperglycemic trigger to first insulin administration. The model information is summarized in Table 3. We initially used the same key variables to start our regression and performed manual backward selection. We eventually came up with another model where, like our logistic regression with SOC as the outcome, we had to force diabetes to stay in the model, as it was not a significant indicator of increased waiting time. This was interesting, given that we found significant differences in time to insulin administration in the individual analysis. Just as interesting was that if we performed our extended Cox regression with just diabetes status as a predictor, diabetes status became significant. However, in our final model, steroid administration on the day of surgery was found to be a significant predictor of time to insulin administration ($p < .0001$). With that factor added in, diabetes status became statistically non-significant ($p = 0.608$), while the hazard ratio for steroids not being administered on the day of surgery compared to steroids being administered was 2.408 (CI = 1.887 - 3.075; $p < .0001$). These results suggest that, when controlling for steroid administration on the day of surgery, there is no statistically significant evidence to support our hypothesis that there is a difference in the average time from hyperglycemic trigger to first insulin administration between diabetes status groups.

Table 3. Summary of Hyperglycemia Trigger Time (Mins) to Insulin Administration Analysis

	Parameter Estimate	Standard Error	P-value	Hazard Ratio	95% Wald Confidence Limits	
Diabetes Status (Without Diabetes)	-0.0648	0.1264	0.6083	0.937	0.732	1.201
Steroids w/i 24 Hours of Surgery (No)	0.8790	0.1246	<.0001	2.408	1.887	3.075

Discussion

The results of our analyses revealed some interesting things; some of which we expected, and some that we did not. In our study cohort, we found the degree of hyperglycemia was similar between hyperglycemic DM patients and hyperglycemic NDM patients. We also discovered that, as we hypothesized, the length of hospital stay was longer for hyperglycemic NDM patients than it was for hyperglycemic DM patients. However, we additionally found that this increase in LOS could not be explained by the appropriateness of treatment by either of two measures: one, whether or not all components of standard of care were met; and two, the length of time from hyperglycemic trigger to first insulin administration.

As we have previously noted, perioperative hyperglycemia has been associated with a variety of adverse outcomes, including morbidity, post-operative infections, increased length of hospital stay, and mortality (DeFelice & Thompson, 2016, Kwon et al, 2013, Umpierrez et al, 2011). We have also noted that increasing blood glucose levels have been shown to be directly associated with increased hospital costs (Furnary, Wu & Bookin, 2004). Other complications associated with perioperative hyperglycemia include acute respiratory failure, pneumonia, acute renal failure, and stroke (Davis et al, 2018). In addition, there are several other examples in the literature that show that perioperative hyperglycemia leads to a greater risk of adverse outcomes in NDM patients when compared to DM patients. NDM patients have a significantly higher risk of adverse events among all patients if they have any level of hyperglycemia in the perioperative period (Kotagal et al, 2015). Also, NDM patients with perioperative hyperglycemia have nearly two times the risk of re-operative interventions, infections, increased length of stay, and in-hospital death than DM patients with this condition (Kwon et al, 2013). Our study seemed to confirm the results of the previously cited research on differences in LOS between diabetes status groups. Our multivariate linear regression with LOS as the outcome showed a significant association with diabetes status. In that analysis, we saw that DM patients had shorter lengths of hospital stay than NDM patients, when controlling for other factors such as standard of care.

We also believe that our study was unique in a couple of areas. None of the studies that we cited or researched controlled for both steroid administration and SOC treatment of hyperglycemia. Also, our full study cohort data set did not include just one type of surgery, as did many of the other studies we reviewed. Indeed, the surrogate for type of surgery (procedure duration in hours) was found to be a significant predictor of LOS in our multivariate linear regression. So, we believe that not only did we support the conclusions of other studies regarding LOS, but we also were able to look at perioperative hyperglycemia through a comparatively different lens.

We have looked at some studies which concluded that there is a difference in adverse outcomes, such as LOS, between patients with and without diabetes. But we have also noted the possible mechanisms as to why NDM patients seem to have worse outcomes from perioperative hyperglycemia. Some of the reasons stem from the differences in physiological response, such as hyperglycemia possibly having a more pronounced effect on those without diabetes because it is a novel stressor to them. Hence, those with diabetes may be more accustomed to the inflammatory/oxidative effect of hyperglycemia. This also points to the idea that the degree of physiological stress necessary to cause hyperglycemia may be greater in NDM patients (Kotagal et al, 2015). We have also touched upon evidence from the literature, such as the study by Kwon et al (2015), which posits that NDM patients might receive hyperglycemia care that is inferior to the care received by DM patients with regards to the timeliness of insulin treatment, the standard of care insulin regimens, and standard blood glucose monitoring.

In our study, standard of care monitoring was examined; which we believe makes ours one of the first studies to address the underlying mechanisms of the differences between DM and NDM patients. Though we did examine the SOC of hyperglycemia treatment, we did not find a statistically significant difference in the SOC received by the diabetes status groups. Management of hyperglycemia may still be the issue; but perhaps it is not the time to SOC blood glucose monitoring and the time to insulin administration that are the key metrics. Perhaps the key issues are more related to the insulin dose, the speed at which blood glucose is brought under control, and/or how well blood glucose is controlled throughout the entire hospital admission. Because we did not find the SOC for hyperglycemia to be significantly different between diabetes status groups, we must conclude that one of the other physiological mechanisms is responsible for the increased LOS for NDM patients.

Limitations

We acknowledge that several limitations to this study should be considered. In our study cohort, we had only hyperglycemic DM and NDM patients. We did not have a comparison group of patients without hyperglycemia. So, we could not address some of the issues discussed, like the degree of physiological stress needed to cause hyperglycemia in NDM patients. There also could have been an issue with selection bias, as we may have missed patients who had hyperglycemia that was never detected during the course of their hospitalization. Also, many of the patients in our study cohort without a formal diabetes diagnosis may in fact have had undiagnosed diabetes. Or, there may have been patients who indeed had diabetes, but did not have a diabetes diagnosis accessible in their medical record. For these patients, there may have been some misclassification bias toward the null hypothesis in all analyses. Other limitations include the fact that we did not study the dose of insulin or the degree of glucose control, which both may be important measures of the effectiveness of hyperglycemia management. Also, since this was a retrospective cohort study, our study design allowed for the possibility of unknown and unmeasured confounders. Finally, our study cohort all came from the Nebraska Medical Center, limiting the generalizability of our study results. Only 48.13% of the DM patients in the cohort received the standard of hyperglycemic care. It may be harder to detect sub-standard care for NDM patients when even more than half of the DM patients are receiving sub-standard care for hyperglycemia as well.

Implications

Our single-center study on clinical care for hyperglycemia management shows that standards of care are not being followed for the majority of patients, regardless of diabetes status. There is opportunity for better adherence to standards of care, which would be expected to result in improvement in outcomes (i.e., decreased mortality) that are important to patients.

We believe that further study on the hypotheses examined herein is warranted at other institutions. Further research should also include the additional metrics of insulin dose, how quickly blood glucose is brought under control, and how well blood glucose is controlled throughout patient stay in the hospital. We also suggest that research into the physiologic mechanisms underlying perioperative hyperglycemia should be undertaken. Important mechanisms to be studied should, at the very least, include looking into the idea that DM patients may be more accustomed to the inflammatory/oxidative effect of hyperglycemia than NDM patients; and the idea that the degree of physiologic stress necessary to cause hyperglycemia may be greater in NDM patients than in DM patients.

Conclusion

Perioperative hyperglycemia is common, even among patients without diabetes. We have provided a litany of examples from the scientific literature that not only point out the host of adverse outcomes that arise from perioperative hyperglycemia; but we have also provided ample evidence that NDM patients experience the worst of these adverse outcomes when compared to DM patients. In this study, we also found that perioperative hyperglycemia results in adverse outcomes (e.g. increased LOS) that affect patients without diabetes to a greater degree than patients with diabetes. Yet, when comparing diabetes status groups, we found no evidence to support that the differences in the management of postoperative hyperglycemia are responsible for the differences in adverse outcomes.

Resources

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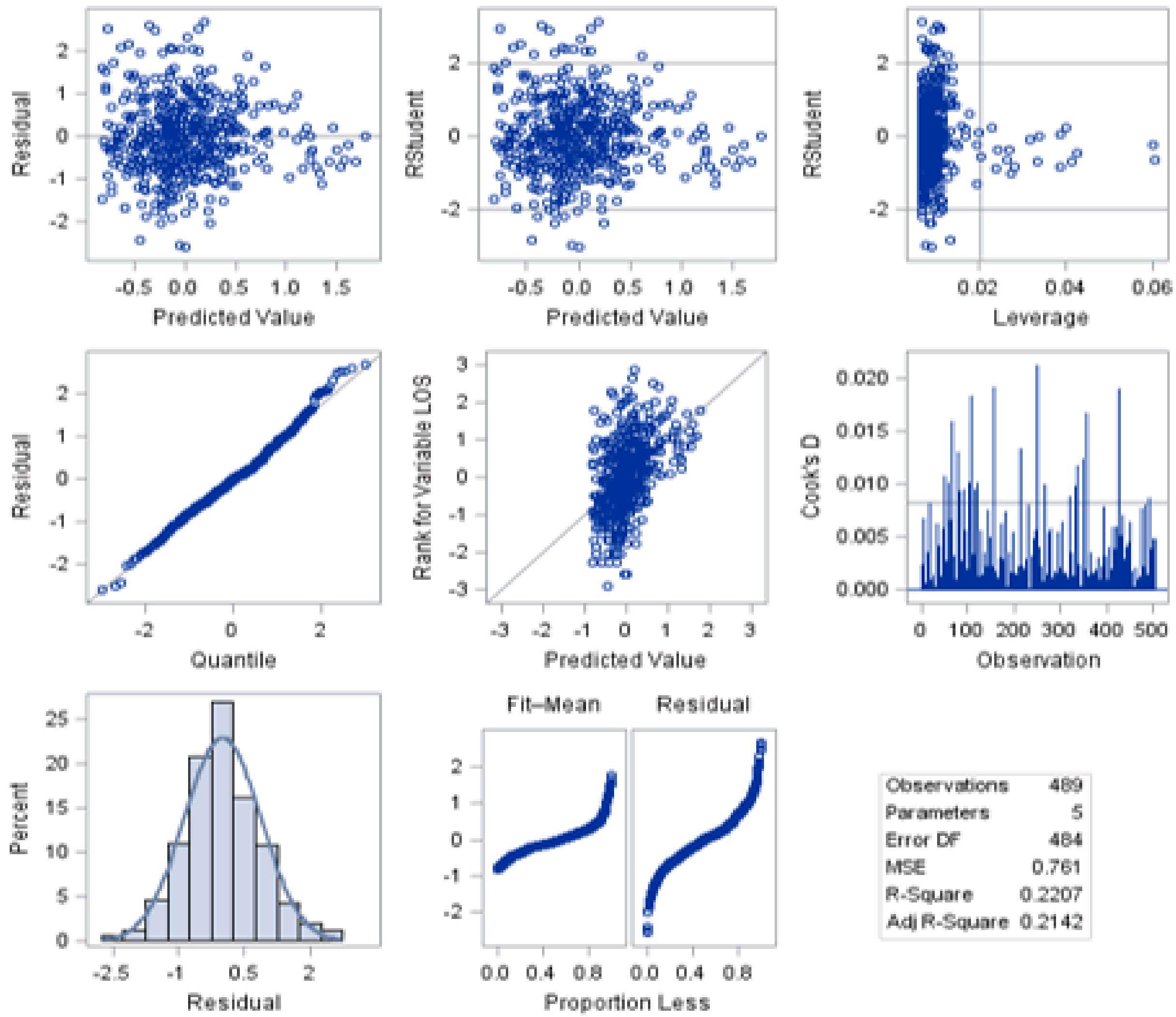
Appendix

Appendix A. Fit Diagnostic Plots for LoS Outcome Multivariate Regression Model



Appendix B. Box Plots for LoS by Diabetes Status